Inhaled Corticosteroids Use and Risk of Invasive Pneumococcal Disease in a Population-based Study

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Abstract

Rationale: The use of inhaled corticosteroids (ICS) is associated with increased pneumonia risk, but the risk of invasive pneumococcal disease (IPD) associated with ICS is not characterized.

Objectives: The aim was to test the hypothesis that the use of ICS increases the risk of IPD.

Methods: Cases were persons 20–65 years of age included in a Swedish national registry of invasive infection caused by *Streptococcus pneumoniae* classified as any IPD as well as the subset of IPD with pneumonia. The case index date was the day the infection was diagnosed. Six control subjects for each case (matched for sex, age, and region) were selected from the Swedish National Population Registry and were assigned the index date of their corresponding case. Current and past users of ICS were defined by the last prescriptions dispensed within 60 or 61–365 days of the index date. Nonusers were defined as those with no dispensed prescription the last 365 days. Current users were characterized by use of fluticasone or budesonide. We used conditional logistic analysis,

including matching and covariates, to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of IPD, IPD with pneumonia, and IPD without pneumonia associated with current or past use of ICS.

Results: Current use of ICS increased the risk for IPD and IPD with pneumonia (OR, 1.71; 95% CI, 1.39–2.10 and OR, 1.94; 95% CI, 1.53–2.47, respectively), but there was no statistical association between current use of ICS and IPD without pneumonia (OR, 1.18; 95% CI 0.78–1.80). Past use of ICS increased the risk for IPD and IPD with pneumonia but not for IPD without pneumonia. Among current ICS users, the odds for IPD were similar for budesonide (OR, 1.34; 95% CI, 1.14–1.57) and fluticasone (OR, 1.41; 95% CI, 1.04–1.90). Among current ICS users, the odds for IPD with pneumonia were slightly higher but of similar magnitude for both budesonide and for fluticasone.

Conclusions: ICS use is associated with an increased risk of IPD and IPD with pneumonia. The risk is driven by IPD with pneumonia. We found similar risks for budesonide and fluticasone.

Keywords: case-control; community-acquired pneumonia; adverse effect

The use of inhaled corticosteroids (ICS) previously has been found to increase the risk of pneumonia (1). Increased risk has been observed among both patients with chronic obstructive pulmonary disease (COPD) and patients with asthma (2, 3). Such risk may vary by type of ICS used; a higher risk has been associated with the use of fluticasone propionate compared with the use of budesonide (4–7). Budesonide, however, also has been associated with pneumonia (8, 9), suggesting that such risk is manifested across a range of corticosteroid potency. Consistent with this view, a Cochrane systematic review from 2014 concluded that there was no statistically significant difference among different ICS in terms of severe pneumonia risk (1).

Streptococcus pneumoniae, an encapsulated gram-positive diplococcus, causes a wide spectrum of human disease, ranging from sinusitis and otitis media to more severe pathologies, including pneumonia in particular (10). Pneumonia caused by *S. pneumoniae* is a common and important cause of morbidity (11). Persons with chronic diseases, such as heart failure, diabetes mellitus, or COPD, are at an increased risk for pneumococcal pneumonia (12–14). Exposure to irritants such as direct and secondhand tobacco smoke and occupational dust and fumes, which may be relevant to COPD and asthma, also may independently increase the risk of pneumonia caused by *S. pneumoniae* (15–17). In pandemic influenza outbreaks, bacterial pneumonia, especially that caused by *S. pneumoniae,* is a severe and well-known bacterial coinfection (18, 19). Severe pneumonia and other serious infections from this organism typically are characterized by invasive pneumococcal disease (IPD), which is defined as pneumococcal bacterial growth cultured from a normally sterile site, such as blood, cerebrospinal fluid, or joint fluid.

In Sweden, cases with IPD (defined as a reported culture of *S. pneumoniae* in blood, cerebrospinal fluid, joint fluid, or other normally sterile body fluids) by mandate must be reported by all microbiological laboratories to a national registry under the aegis of the Swedish National Public Health Agency. Exploiting this registry, we wished to test the hypothesis that the use of ICS increased the risk of IPD. We did so by interrogating this registry and further linking such cases and population-based control subjects to a separate national database capturing medication prescribing to identify ICS use.

Methods

We limited cases with IPD included in this analysis to those aged 20–65 years of age from July 1, 2006, to December 31, 2014. The isolation of *S. pneumoniae* from normally sterile body fluids (e.g., blood or cerebrospinal fluid), detection of *S. pneumoniae* nucleic acid from normally sterile body fluids, or detection of *S.* antigen from normally sterile body fluids were required to be defined as a case of IPD. We extracted data from the IPD registry for the personal identity number, the type of sample, and the index date when the sample was obtained. We randomly selected six control subjects without IPD from the Swedish National Population Registry matched for sex, age (case year of birth), and region of residency. We assigned each control subject the index date of their corresponding case.

We used the personal identification numbers for linkages to all other national registries we interrogated. Prescription medications dispensed by all pharmacies are reported on the individual level to the Swedish Prescribed Drug Registry. We linked cases and control subjects for medication dispensing noted in the Drug Registry for ICS alone or in-combination products. We defined ICS by the following Anatomical Therapeutic Chemical (ATC) codes: R03BA01, R03BA02, R03BA05, R03BA07 and R03BA08 as well as the combined inhalers R03AK06, R03AK07, R03AK08, R03AK09, R03AK10 and R03AK11. Budesonide was defined as R03BA01, R03BA02, and R03AK07; fluticasone was defined as R03BA05, R03AK06, R03AK10, and R03AK11; beclomethasone was defined as R03AK08; mometasone was defined as R03BA07; and ciclesonide was defined as R03BA08.

We defined subjects as current ICS users if the last dispensed prescription was within 60 days of the index date and defined past users those whose last dispensed prescription was between 61 and 365 days before the index date (5). We defined nonusers as those with no dispensed prescription the last 365 days before the index date. We further characterized current users as users of fluticasone, budesonide, or other ICS (mometasone, ciclesonide, or beclomethasone).

We extracted information on prescriptions dispensed for oral corticosteroids (ATC code H02A) and immune-modulating medications (ATC code L03 – L04) if occurring at any time within 5 years preceding the index date. We also identified provision of a pneumococcal vaccination (ATC code J07A L01, J07A L02 and J07A L52). We excluded all otherwise eligible cases and control subjects who has been dispensed a prescription for antibiotics within 30 days before the index date, as that could indicate earlier treatment for a pneumonia.

We used the Swedish National Hospital Discharge Registry to identify hospitalization for any pneumonia, including any hospital stay that included the index date ±7 days. We also used the Swedish National Hospital Discharge Registry to identify the following comorbid conditions based on *International Classification of Diseases, Tenth Revision* (ICD-10) coding: COPD (ICD10 J43-J44), asthma (J45 – J46), diabetes mellitus (E10 – E14), kidney and liver diseases (N00-N08, N10-N12, K70-K77), ischemic heart disease (I20-I25), or cancer (C00-C97), preceding the index date. Using the hospitalization and death registries, we further identified a "pneumonia" subset of IPD with hospitalization or death with any bacterial pneumonia code. We also defined a subset of IPD not diagnosed with pneumonia, "IPD without pneumonia." We extracted information from the Swedish national socioeconomic database on the highest educational level obtained, categorized as follows: pre–high school; high school; or university examination. Based on multiple data bases, we defined ethanol abuse as either hospitalization for alcohol abuse disorder or prescriptions dispensed for drugs used in alcohol dependence at any time within 5 years before index date (ATC code N07BB comprising disulfiram, calcium carbimide, acamprosate, naltrexone, and nalmefen).

We used conditional logistic regression to calculate odds ratios (ORs) of the associations between ICS use (current or past vs. nonuse) and different categorizations of IPD (IPD, IPD with pneumonia, and IPD without pneumonia). We performed separate analyses for ICS and different ICS types (referents matched for age, sex, and region of residence) including

the following covariates: oral steroids or immune-modulating medication use in past 5 years, comorbid conditions (COPD, asthma, kidney and liver diseases, ischemic heart disease, cancer, and diabetes), education, and ethanol abuse. We repeated key analyses stratified by sex. We also performed a sensitivity analysis, modeling the use of ICS through the last 5 years and the risk of IPD or IPD with pneumonia, adjusting for all covariates.

All analyses were performed using SAS version 9.4 M5 (SAS Institute). The Gothenburg Committee of Ethics approved the study (Dnr 729–16).

Results

We identified 5,653 eligible IPD cases with valid personal identity numbers and 33,918 matched referents. After exclusions, 4,128 cases with IPD and 24,142 matched control subjects remained. Among cases, the IPD-positive biological samples were from blood or serum (92.4%) or cerebrospinal fluid (4.7%), with the remainder from other sources, such as joint fluid, ascites, or pleural fluid (2.9%). There were 2,940 cases (71.2%) with pneumonia (IPD with pneumonia) and 1,188 cases (28.8%) with IPD without pneumonia. Among the IPD cases, the prevalence of current use of any ICS was 7.2% ($n = 297$); by subtypes, this included 11.2% budesonide ($n = 464$), 2.8% fluticasone ($n = 116$), and 0.2% other ICS ($n = 48$). Among the control subjects, the corresponding current use of any ICS was 5.2% ($n = 1261$); by subtypes, this included 4.2 % budesonide ($n = 1024$), 0.8% fluticasone ($n = 189$), and 0.2% other ICS ($n = 48$). Only 14 (0.3%) of the cases with IPD had documentation of a pneumococcal vaccination. Additional details on demographics, comorbid conditions, and corticosteroid use are shown in Table 1.

In models, taking into account sex, age, and geographic region (the matching criteria), the current use of ICS was associated with an increased risk of IPD (OR, 3.99; 95% CI, 3.43–4.64), IPD with pneumonia (OR, 4.68; 95% CI, 3.93–5.57), and IPD without pneumonia (OR, 2.51; 95% CI, 1.84–3.42) (Table 2). In models fully adjusted for covariates, however, the ORs were considerably attenuated but remained elevated and statistically significant for IPD (OR, 1.71; 95% CI, 1.39–2.10) and IPD with pneumonia (OR, 1.94; 95% CI, 1.53–2.47)

(Table 2). There was no statistical association after adjustment between either current or past use of ICS and IPD without pneumonia (OR, 1.18; 95% CI, 0.78–1.80 and OR, 1.04; 95% CI, 0.73–1.48, respectively) (Table 2).

Among current ICS users, the odds for IPD were similar for budesonide (OR, 1.34; 95% CI, 1.14–1.57) and fluticasone (OR, 1.41; 95% CI, 1.04–1.90). The odds for IPD with pneumonia were slightly higher but of similar magnitude, and they were statistically significant for both budesonide (OR, 1.46; 95% CI, 1.21–1.77) and fluticasone (OR, 1.56; 95% CI, 1.10–2.23). (Table 3).

In stratified analyses, the odds for IPD in relation to the current use of ICS were similar for men and women (Table 4). Among men, however, the odds for IPD in relation to prior use of ICS were increased compared with women.

In a sensitivity analysis, any use of ICS the last 5 years (rather than 1 yr only) remained associated with an increased risk of IPD: (OR, 1.45; 95% CI, 1.18–1.77) and IPD with pneumonia (OR, 1.62; 95% CI, 1.28–2.06).

Discussion

This population-based, case-control study provides new evidence that ICS use is a risk factor for IPD, supporting and clarifying relationships previously observed in relation to severe pneumonia. Importantly, in previous reports, this risk was not defined by IPD, a more definitive confirmation of serious infection. Also of note, we did not observe an increased ICS-associated risk of IPD when pneumonia was not present. There was no substantive difference in risk for the two most commonly prescribed types, with fairly similar estimated odds of disease for fluticasone and budesonide.

The risk of pneumonia is generally believed to be increased among smokers and among persons with COPD, and importantly, this risk seems to increase among ICS users with such characteristics (2). Furthermore, such risk increases with increasing doses of ICS. The current study, however, is the first to identify an association between ICS use and risk of IPD, in particular IPD with pneumonia. The outcome in the current study, IPD, is typically characteristic of severe disease requiring hospitalization, which also means

that the outcome of IPD with pneumonia is a condition comparable with severe pneumonia. The results also clearly indicate that the results are driven by increased risk for IPD with pneumonia. IPD without pneumonia did not show increased odds. A weakness in our study is that although we had temporal prescribing data, we had no data on the prescribed doses of ICS. Studies of pneumonia (but not IPD) have reported a dose response, with increasing odds with increasing doses of ICS (1, 5).

We did not observe differential risk by types of ICS. This is consistent with a Cochrane report from 2014 that concluded that both fluticasone and budesonide were associated with similar risks for severe pneumonia requiring hospitalization. In that regard, it is interesting to note that the same Cochrane report concluded that the risk of less serious pneumonia (treated outside hospital) was significantly higher for fluticasone compared with budesonide. A later case-control study from a cohort of people with asthma found that the odds for pneumonia or acute lower respiratory tract infections were increased both in relation to the use of budesonide (OR, 1.20; 95% CI, 1.06–1.35) and the use of fluticasone (OR, 1.64; 95% CI, 1.50–1.79) (20). In a Canadian nested case-control study of a cohort of patients with COPD, increased odds of serious (hospitalized) pneumonia were observed for both fluticasone and budesonide, albeit with higher odds for fluticasone (5). A study based on a cohort of people with asthma found increased odds of hospitalized pneumonia both in relation to budesonide (OR, 2.67; 95% CI, 2.05–3.49) and in relation to fluticasone (OR, 1.93; 95% CI, 1.58–2.36) (8). Our observation of similar risks for budesonide and fluticasone support the view that in terms of severe pneumonia, the type of ICS may be less important than other factors.

The mechanism for ICS increased risk for IPD and IPD with pneumonia is not clear. Multiple studies have observed potentially relevant adverse effects of local inhaled steroids, including the suppression of alveolar macrophages, impaired release of proinflammatory cytokines, and impaired pulmonary clearance of pathogens, which together may result in impaired host defense in the respiratory tract (21, 22). Comorbid conditions such as obstructive airway diseases (COPD and asthma) also may increase pneumonia risk because of their inherent inflammatory attributes. As a

Table 1. Characteristics of cases with IPD and matched control subjects from the general population of Sweden

Characteristics	IPD (n = 4,128)			All Control Subjects (N = 24,142)
	All IPD (N = 4,128)	**IPD with Pneumonia (n = 2,940)**	**IPD without Pneumonia (n = 1,188)**	
Sex, M, n (%)	2,175 (52.7)	1,560 (53.1)	615 (51.8)	12,766 (52.9)
Age, yr (SD)	53.4 (10.9)	53.3 (10.8)	53.8 (10.8)	52.3 (11.4)
Completed university exam, n (%)	1,007 (24.4)	686 (23.3)	321 (27.2)	8,080 (33.5)
Inhaled corticosteroids, n (%)				
Current users	297 (7.2)	237 (8.1)	60 (5.1)	1,781 (5.3)
Past users	280 (6.8)	208 (7.1)	72 (6.1)	1,005 (3.0)
Nonusers	3,551 (86.0)	2,495 (84.9)	1,056 (88.9)	21,356 (88.5)
Dispensing or diagnosis within 5 yr preceding the index date, n (%)				
Oral corticosteroids	716 (17.3)	461 (15.7)	255 (21.5)	1,133 (4.7)
Immune-modulating drugs*	307 (7.4)	186 (6.3)	121 (10.2)	378 (1.6)
Pneumococcal vaccination	14 (0.3)	6 (0.2)	8 (0.7)	13 (<0.1)
COPD	379 (9.2)	303 (10.3)	76 (6.4)	207 (0.9)
Bronchial asthma	342 (8.3)	271 (9.2)	71 (6.0)	545 (2.3)
Diabetes mellitus	548 (13.3)	401 (13.6)	147 (12.4)	629 (2.6)
Kidney and liver diseases	124 (3.0)	84 (2.9)	40 (3.4)	177 (0.7)
IHD	231 (5.6)	158 (0.4)	73 (6.1)	619 (2.6)
Cancer	547 (13.3)	291 (9.9)	256 (21.5)	246 (1.0)
Ethanol abuse	390 (9.4)	284 (9.7)	106 (8.9)	337 (1.4)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; IHD = ischemic heart disease; IPD = invasive pneumococcal disease; SD = standard deviation.
*See METHODS for definition.

potential causal pathway for inflammatory lung disease independent of pharmacological effects, the use of inhaled steroids would simply be a marker of the underlying condition. When we adjusted for asthma and COPD, however, the ICS-associated risk we observed was attenuated but not eliminated. Moreover, the diagnoses of asthma and COPD we used in this study are based on those obtained in hospital settings and thus more applicable to asthma and COPD likely to be of greater disease severity.

This study has both strengths and limitations. Central to our analysis is the powerful resource of a national Swedish IPD surveillance, although this also means that we are not in a position (because of the case-control design) to similarly study other invasive infections. Other major strengths are that we have been able to use national registry data to assess the use of ICS andthat we were able to use data from national registries to control for the use of oral steroids and other immune-modulating drugs. Another strength is that the medication data was based on drugs

Table 2. Crude and adjusted ORs of IPD, IPD with pneumonia, and IPD without pneumonia associated with current or past use of ICS in a national register-based case-control study

ICS Dispensing within 12 mo Preceding the Index Date	All IPD (N = 4,128)		IPD with Pneumonia (n = 2,940)		IPD without Pneumonia (n = 1,188)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Current users vs. nonusers						
Model 1*	3.99	3.43–4.64	4.68	3.93–5.57	2.51	1.84–3.42
Model 2†	1.71	1.39–2.10	1.94	1.53–2.47	1.18	0.78–1.80
Past users vs. nonusers						
Model 1*	2.45	2.13–2.83	2.69	2.27–3.18	1.95	1.49–2.57
Model 2†	1.22	1.01–1.47	1.30	1.04–1.63	1.04	0.73–1.48

Definition of abbreviations: CI = confidence interval; ICS = inhaled corticosteroids; IPD = invasive pneumococcal disease; OR = odds ratio.
*Conditional logistic regression with matching for sex, age, and place of residency.
†Conditional logistic regression with matching for sex, age, and place of residency and adjustments for educational level, ethanol abuse, use of oral corticosteroids, use of immune-modulating drugs, and diagnosis of chronic obstructive pulmonary disease, asthma, kidney and liver diseases, ischemic heart disease, cancer, and diabetes.

Table 3. Crude and adjusted ORs of IPD, IPD with pneumonia, and IPD without pneumonia associated with current use of ICS (vs. nonuse) in a national register-based case-control study by drug type

Current Use vs. Nonuse	All IPD (N = 4,128)		IPD with Pneumonia (n = 2,940)		IPD without Pneumonia (n = 1,188)	
	OR	95% CI	OR	95% CI	OR	95% CI
Fluticasone						
Model 1*	3.67	2.91–4.65	4.48	3.42–5.87	2.01	1.22–3.32
Model 2†	1.41	1.04–1.90	1.56	1.10–2.23	1.08	0.58–2.02
Budesonide						
Model 1*	2.88	2.56-3.23	3.21	2.80–3.67	2.14	1.70–2.69
Model 2†	1.34	1.14–1.57	1.46	1.21–1.77	1.04	0.76–1.41
Other users						
Model 1*	1.46	0.77–2.76	1.42	0.69–2.95	1.59	0.43–5.83
Model 2†	0.49	0.22–1.09	0.30	0.12–0.81	1.71	0.41–7.11

Definition of abbreviations: CI = confidence interval; ICS = inhaled corticosteroids; IPD = invasive pneumococcal disease; OR = odds ratio.
*Conditional logistic regression with matching for sex, age, and place of residency.
†Conditional logistic regression with matching for sex, age, and place of residency and adjustments for educational level, ethanol abuse, use of oral corticosteroids, immune-modulating drugs, and diagnosis of chronic obstructive pulmonary disease, asthma, kidney and liver diseases, ischemic heart disease, cancer, and diabetes.

dispensed, not only on those prescribed. We also adjusted for level of education as a proxy for socioeconomic status. Abuse of alcohol is another risk factor for IPD that we took into consideration, using a composite variable for adjustment subsuming either a diagnosis of ethanol abuse disorder or dispensing medications used to treat alcohol dependence, mainly disulfiram aversion therapy.

Still, residual confounding from unmeasured covariates, especially "confounding by indication" may still be present. We have tried to adjust for this possible bias by adjusting for a number of comorbidities and socioeconomic factors. We have also excluded all subjects with antibiotics prescribed within 30 days before the index date because this could indicate therapy for pneumonia (5). Nonetheless, confounding by indication cannot be excluded.

There are also a number of important limitations of the study. One major limitation is that we, as previously mentioned, lack information about the prescribed doses of ICS. It is also important to stress that we did not have information about the smoking habits in the population studied and thus could not directly adjust for this in our modellings. This is an important study limitation that should temper the interpretation of our findings. Smoking has been shown to be a risk factor for pneumonia and death from pneumococcal pneumonia (23). In Sweden, the prevalence of current smoking in the age group 50–65 is approximately 18%, making smoking an unlikely confounder sufficiently

Table 4. Crude and adjusted ORs of IPD, IPD with pneumonia, and IPD without pneumonia associated with current or past use of ICS in a national register-based case-control study among men and women

ICS Dispensed within 12 mo of Index Event	All IPD		IPD with Pneumonia		IPD without Pneumonia	
	OR	95% CI	OR	95% CI	OR	95% CI
Women						
Current users vs. nonusers						
Model 1*	4.23	3.48–5.14	5.11	4.07–6.41	2.46	1.65–3.67
Model 2†	1.75	1.34–2.28	2.01	1.48–2.75	1.22	0.71–2.10
Past users vs. nonusers						
Model 1*	2.30	1.90–2.78	2.69	2.15–3.35	1.57	1.09–2.27
Model 2†	1.13	0.88–1.44	1.29	0.96–1.72	0.83	0.52–1.33
Men						
Current users vs. nonusers						
Model 1*	3.66	2.89–4.64	4.13	3.14–5.42	2.56	1.57–4.17
Model 2†	1.64	1.18–2.28	1.86	1.27–2.73	1.09	0.55–2.16
Past users vs. nonusers						
Model 1*	2.69	2.16–3.35	2.70	2.09–5.42	2.64	1.75–3.99
Model 2†	1.37	1.02–1.85	1.32	0.92–1.88	1.54	0.89–2.67

Definition of abbreviations: CI = confidence interval; ICS = inhaled corticosteroids; IPD = invasive pneumococcal disease; OR = odds ratio.
*Conditional logistic regression with matching for age and place of residency.
†Conditional logistic regression with matching for age and place of residency and adjustments for educational level, ethanol abuse, use of oral corticosteroids, immune-modulating drugs, and diagnosis of chronic obstructive pulmonary disease, asthma, kidney and liver diseases, ischemic heart disease, cancer, and diabetes.

common to explain the associations that we observed, even if smokers were more likely than never-smokers to be dispensed ICS (24). Moreover, the inclusion of socioeconomic status may, to some extent, adjust for current or past smoking, given that low socioeconomic status is associated with smoking in high-income countries (25). We also adjusted for severe COPD, which is strongly linked to cumulative smoking, as well as other chronic diseases for which smoking is a well-established risk factor. Thus, collectively, these covariates do serve as partial surrogates for smoking. The study covered the age range of 20–65 years; hence, our results cannot be generalized to children and teenagers or older adults.

In Sweden, at the time of the present study, pneumococcal vaccination was recommended for all persons over 65 years but only for certain other risk groups of younger age, such as persons with chronic heart, lung, and kidney diseases (26). Smoking alone is not an indication for pneumococcal vaccination in Sweden (26). Our data (Table 1) show that the prevalence of pneumococcal vaccination was very low among both the cases and the referents. Importantly, the findings of this study support consideration of ICS as a potential new indication for pneumococcal vaccination, especially under the age of 65 years. This may be of even further

importance among those already recognized as susceptible groups, such as persons with the chronic conditions we considered as covariates, although we did not specifically study that potential interaction because of a lack of sufficient disease-specific observations.

In conclusion, although residual confounding cannot be ruled out entirely, ICS use is associated with increased risk of IPD and IPD with pneumonia. The risk is driven by IPD with pneumonia. We found similar risks for budesonide and fluticasone. ∎

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